

(43) International Publication Date
27 September 2012 (27.09.2012)

- (51) **International Patent Classification:**
A01N 31/14 (2006.01) *A61K 31/075* (2006.01)
- (21) **International Application Number:**
PCT/IN2011/000203
- (22) **International Filing Date:**
24 March 2011 (24.03.2011)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (71) **Applicant (for all designated States except US):** **SYMED LABS LIMITED** [IN/IN]; 8-3-166/6&7, II Floor, Sree Arcade, Erragadda, Andhra Pradesh, Hyderabad 500018 (IN).
- (72) **Inventors; and**
- (75) **Inventors/Applicants (for US only):** **MOHAN RAO, Dodda** [IN/IN]; 8-2-293/82/A/202, D.No.: 202, Opp. Jubilee international club, Road No. 14, Jubilee Hills, Andhra Pradesh, Hyderabad 500033 (IN). **KRISHNA REDDY, Pingili** [IN/IN]; H.No.: 13-1-183/1, Plot No. 69, Snehapuri colony, Borabanda, Andhra Pradesh Hyderabad 500018 (IN). **ANNA REDDY, Ambati** [IN/IN]; H.No.: 1-118, Kachapur, Shankarapatnam, Andhra Pradesh, Karimnagar 505470 (IN).
- (81) **Designated States (unless otherwise indicated, for every kind of national protection available):** AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

- (84) **Designated States (unless otherwise indicated, for every kind of regional protection available):** ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

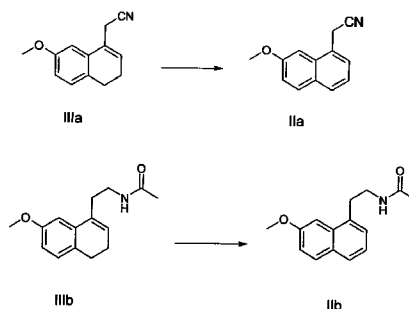
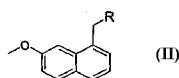
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- of inventorship (Rule 4.17(iv))

Published:

- with international search report (Art. 21(3))

(54) **Title:** PROCESSES FOR THE PREPARATION OF INTERMEDIATES OF N-[2-(7-METHOXY-1-NAPHTHYL) ETHYL] ACETAMIDE

Symeds labs limited

**Fig. 1**Where R is C $\equiv$ N, CH₂-NH-COCH₃

(57) **Abstract:** The present invention provides processes for the preparation of intermediates of N-[2-(7-methoxy-1-naphthyl) ethyl] acetamide. More particularly the present invention relates to processes for the preparation of the compound of structural formula II. Also provides Isolated solid (7-Methoxy-1-naphthyl)ethanamine compound of structural formula VI as freebase.

SLLPCT16

PROCESSES FOR THE PREPARATION OF INTERMEDIATES OF N-[2-(7-METHOXY-1-NAPHTHYL) ETHYL] ACETAMIDE

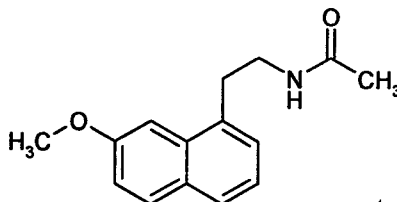
BACKGROUND OF THE INVENTION

1. Technical field:

The present invention relates to processes for the preparation of intermediates of N-[2-(7-methoxy-1-naphthyl) ethyl] acetamide.

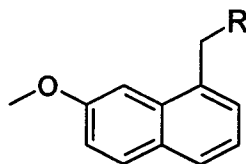
Brief description of the related art:

Agomelatine is an agonist of melatoninergetic system receptors and an antagonist of the 5-HT_{2C} receptor. Those properties confer activity in the central nervous system and, more especially, in the treatment of severe depression, seasonal affective disorders, sleep disorders, cardiovascular pathologies, and pathologies of the digestive system, insomnia and fatigue resulting from jetlag, appetite disorders and obesity. Agomelatine is under regulatory review in US and is being approved in EU for the treatment of major depressive disorder. It is marketed under the trade names Valdoxan, Melitor, Thymanax in the form of tablets in dosage strength 25 mg. Agomelatine is chemically described as N-[2-(7-methoxy-1-naphthyl)ethyl]acetamide (herein after referred by generic name agomelatine) and is represented by the structural formula I



I

More particularly the present invention relates to processes for the preparation of the compound of structural formula II



II

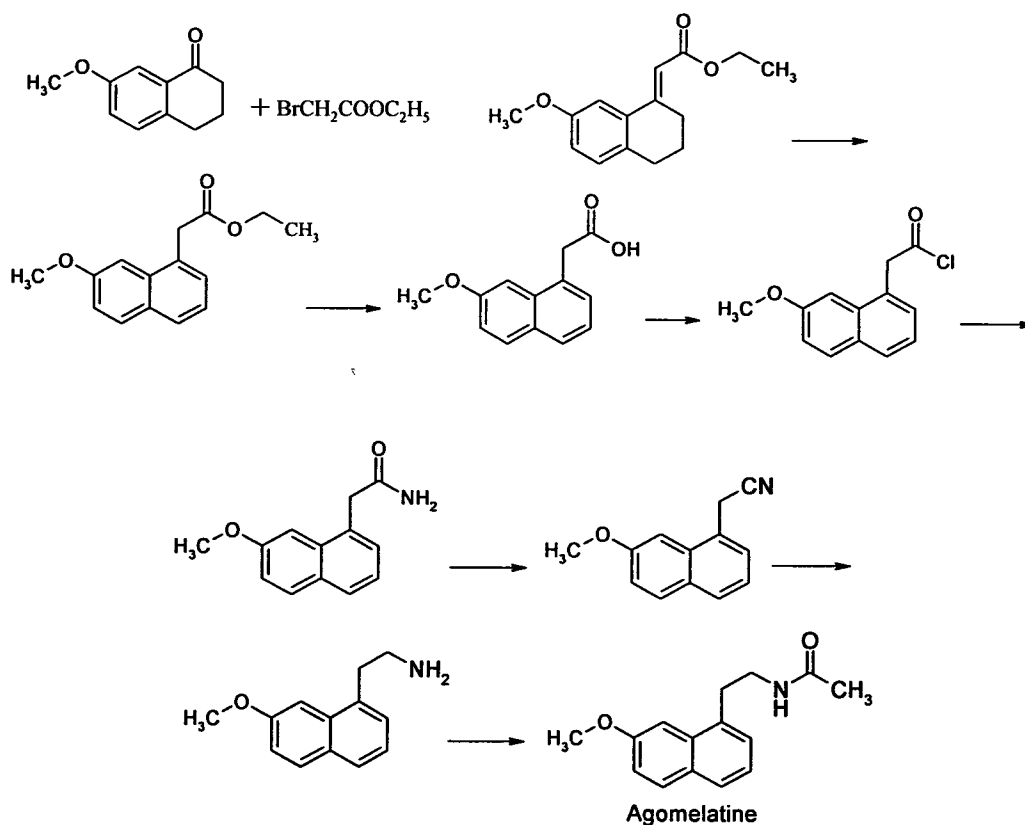
Where R is $\text{C}\equiv\text{N}$, $\text{CH}_2\text{-NH-COCH}_3$

SLLPCT16

U.S. Patent No. 5,225,442 describes agomelatine, a pharmaceutical composition, a method of treatment, and a process for the preparation thereof.

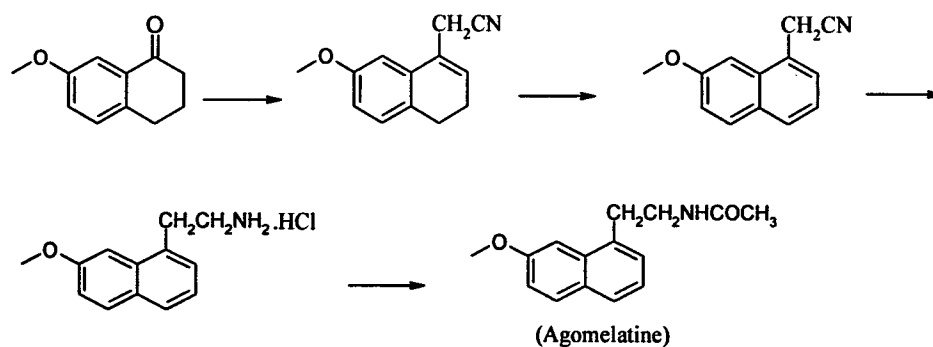
US '442 disclose a process for the preparation of agomelatine which is illustrated by the below scheme:

5



U.S. Patent No. US 7,544,839 describes the preparation of agomelatine as illustrated by below scheme :

10



Aforementioned processes uses expensive reagents like palladium-carbon in addition to allyl compounds and involve prolong reaction time periods thus rendering the processes expensive and do not comply with industrial requirements in terms of cost and the

SLLPCT16

environment. Hence, there is a need for an improved process for the preparation of intermediates of agomelatine, which can avoid the use of hazardous and expensive chemicals thus reducing the formation of process related impurities and related purification steps.

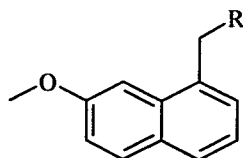
In view of the pharmaceutical value of this compound, it is important to be able to obtain by cost effective and simple processes that are readily amenable on industrial scale and that results in agomelatine in a good yield and with excellent purity.

The processes of present invention are simple, eco-friendly, inexpensive, reproducible, and robust and feasible on an industrial scale.

SUMMARY OF THE INVENTION

The present invention relates to processes for the preparation of intermediates of N-[2-(7-methoxy-1-naphthyl) ethyl] acetamide (I).

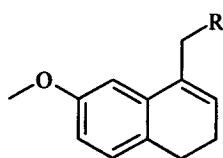
In one aspect, the present invention relates to a process for the preparation of intermediate compound of formula II

**II**

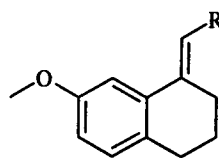
Where R is $C\equiv N$, $CH_2-NH-COCH_3$

comprising:

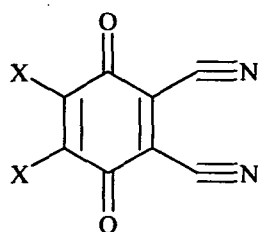
subjecting the compound of formula III

**III**

or

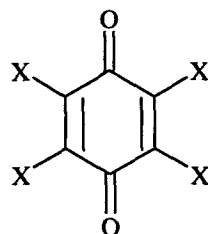
**III**

Where R is same as defined above to aromatization by reacting with a quinone derivative of formula IV

SLLPCT16

IV

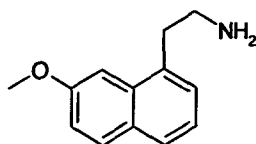
Where X is halogen atom (F, Cl, Br, I)
or formula V



V

Where X is same as defined above
or selenium metal to afford the compound of formula II.

In another aspect, the present invention relates to isolated solid (7-Methoxy-1-naphthyl)
ethanamine compound of structural formula VI as free base.



VI

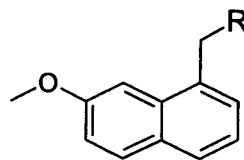
BRIEF DESCRIPTION OF THE DRAWING

Fig. 1: is a schematic representation of the processes of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to processes for the preparation of intermediates of N-[2-(7-methoxy-1-naphthyl) ethyl] acetamide (I).

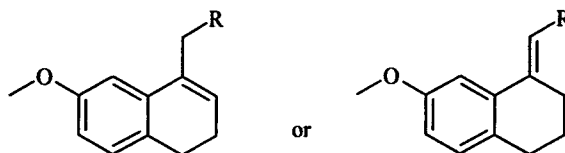
In one embodiment of the present invention, there is provided a process for the preparation of intermediate compound of formula II

SLLPCT16**II**

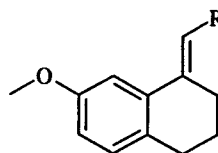
Where R is $C\equiv N$, $CH_2-NH-COCH_3$

comprising:

- 5 subjecting the compound of formula III

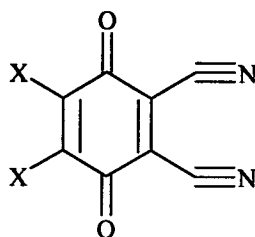


or

**III****III**

Where R is same as defined above

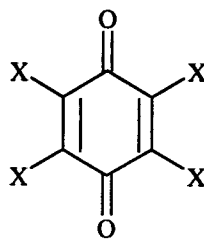
to aromatization by reacting with a quinone derivative of formula IV

**IV**

10

Where X is halogen atom (F, Cl, Br, I)

or formula V

**V**

- 15 Where X is same as defined above

or selenium metal to afford the compound of formula II.

The suitable aromatization reagents include but are not limited to quinone derivatives such as compounds of formula IV or V where X is halogen atom like F, Cl, Br, and I which include

SLLPCT16

DDQ, p-chloranil, p-bromanil, p-floranil, 2,3-dibromo-5,6-dicyano benzoquinone, 2,3-dicyano-4-chlorobenzoquinone, 2,3-dicyanobenzoquinone and other quinone derivatives such as 1,2-benzoquinones, 1,3-benzoquinones, o-chloranil, o-bromanil, o-floranil and the like or mixtures thereof, preferably DDQ or p-chloranil.

- 5 The molar ratio of aromatization reagent to the compounds of formula (III) can be from about 5:1 to about 1:1, preferably 1:1.

The organic solvents that can be used include but are not limited to halogenated solvents such as dichloromethane, ethylene dichloride, chloroform, chlorobenzene and the like; esters such as ethyl acetate, isopropyl acetate, tertiary butyl acetate and the like; hydrocarbon
10 solvents such as n-hexane, n-heptane, cyclohexane, toluene, o-xylene, p-xylene and the like; ethers such as tetrahydrofuran, 1,4-dioxane, diethyl ether and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), N,N-dimethylacetamide (DMA), N-methyl pyrrolidone (NMP), ethylene glycol and the like; or mixtures thereof in various proportions without limitation. Preferably the hydrocarbon solvent toluene or o-xylene
15 is being used.

The reaction is optionally performed in the absence of organic solvents.

The reaction temperature and the time should be suitable to bring the reaction to completion at a minimum time, without the production of unwanted side products. In general, it is convenient to carry out the reaction at a temperature of from about 35°C to about reflux
20 temperatures of the solvents used. Preferably at reflux temperatures of the solvents used. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagent and solvent employed. However, provided that the reaction is effected under the preferred conditions discussed above, a period from about 1 hour to about 15 hours, preferably from about 5 hour to 10 hours.

25 After completion of the reaction, the desired compounds can be obtained from the reaction mixture by conventional means known in the art. For example, the working-up of reaction mixtures, especially in order to isolate desired compounds, follows customary procedures, known to the organic chemists skilled in the norms of the art and steps, e.g. selected from the group comprising but not limited to extraction, neutralization, crystallization,
30 chromatography, evaporation, drying, filtration, centrifugation and the like.

The intermediate compounds of formula II obtained by the process of present invention are optionally purified either by converting into respective acid addition salts or by

SLLPCT16

recrystallization using the solvents or mixture of solvents or their aqueous mixtures or by slurry in the customary solvents.

Advantageously the processes of present invention is of particular interest for the following reasons it allows the compound of formula (II), exclusively, to be obtained on an industrial scale. This result is altogether surprising is due to the use of cheaper and simple reagents like DDQ and chloranil unlike palladium –carbon. The rate of conversion of the compound of formula (III) to the compound of formula (II) is very high, exceeding 80%, unlike that which could be observed using palladium carbon, for which the rate does not exceed 75% whereas the use of quinone derivatives like DDQ or chloranil are entirely compatible with industrial requirements in terms of cost and the environment unlike hydrogenation catalyst for the conversion of the compound of formula (III) to the compound of formula (II) currently used. Furthermore, it allows the compound of formula (II), exclusively, in particular free from the corresponding impurities.

Finally, the observed rates of conversion of the compounds of formula (III) to the compounds of formula (II) are high, exceeding 80%. hydrogenation of the compound using palladium–carbon or Raney nickel described in the prior art requires conditions that are difficult to apply on an industrial scale and the final yield is less than 70%. Furthermore, a principal drawback of that reaction is the concomitant formation of the "bis" compound and the difficulty of controlling the conversion rate of that impurity. The process developed by the Applicant allows the compounds of formula (II) to be obtained with a level of impurity down to below 1% under experimental conditions that are compatible with industrial requirements. The reported processes in the literature for the preparation of agomelatine or its intermediates results in the formation of various impurities and bye products leading to keep several purification steps intermittently at various stages thus resulting in very poor yields and purities of the intermediates and final product.

Advantageously, the processes of present invention provides the compound of formula I from intermediate compound of formula II by using quinone derivatives of formula IV or V like DDQ or chloranil resulted in tremendous improvement in the yields and purities which ultimately lead to the higher yields and purities of final product. Moreover the present process is very cost effective, reproducible and more viable on commercial scale.

Additionally the quinone derivatives described above can be recovered, recycled and reused thus making the process of present invention more economic.

SLLPCT16

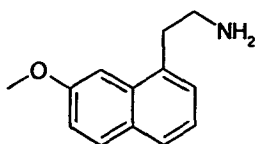
The molar ratio of selenium to the compound of formula (III) can be from about 5:1 to about 1:1, preferably 1:1.

The conversion of compound of formula III to the compound of formula II by aromatization using selenium is carried out in the absence of solvents and optionally in the presence of solvents as described above.

The reaction temperature and time when selenium is being used as reagent can be from about 100°C to about 250°C, preferably at a temperature of from about 215°C to about 220 °C. The time required is from about 1 hour to about 10 hours, preferably from about 3 to 5 hours.

Advantageously, the processes of present invention described herein produces the intermediates and the final product in high yields and purities than the processes reported in the literature that too using simple and cost effective industrially applicable processes.

In another embodiment of the present invention, there is provided isolated solid (7-Methoxy-1-naphthyl)ethanamine compound of structural formula VI as free base.

**VI**

The isolated solid (7-Methoxy-1-naphthyl)ethanamine (VI) is pure. Preferably it has about 95% purity by weight with respect to other compounds. Preferably, the (7-Methoxy-1-naphthyl)ethanamine of formula VI is isolated in about 99% purity by weight. Thus, the isolated solid (7-Methoxy-1-naphthyl)ethanamine contains less than about 2%, preferably less than about 1% by weight of impurities by HPLC.

The isolated solid (7-Methoxy-1-naphthyl)ethanamine (VI) of the present invention is prepared and isolated by the process substantially as described in example 9.

The solid 7-Methoxy-1-naphthyl)ethanamine (VI) is prepared either from its respective acid addition salt for example hydrochloric acid salt by using an organic or inorganic base in the presence of organic solvents or directly by free base using conventional techniques like crystallization from solvents or their mixtures or their aqueous mixtures thereof or by solvent-antisolvent technique.

The solvents that can be used for the isolation of compound of formula VI as solid include but are not limited alcohols such as methanol, ethanol, n-propanol, isopropanol, n-

SLLPCT16

butanol, isobutanol, and tertiary butyl alcohol and the like; halogenated solvents dichloromethane, ethylene dichloride, chloroform and the like; ketonic solvents such as acetone, methyl ethyl ketone, methyl isobutyl ketone, 2-butanone and the like; nitrile solvents such as acetonitrile, propionitrile and the like; esters such as ethyl acetate, isopropyl acetate and the like; hydrocarbons such as toluene, o-xylene, cyclohexane and the like or mixtures thereof in various proportions without limitation. Preferably, ethyl acetate.

The antisolvents include, but are not limited to water, hydrocarbon solvents such as n-hexane, n-heptane, cyclohexane, petroleum ether, toluene and the like; ethers such as diethyl ether, diisopropyl ether, methyl tertiary butyl ether, and the like or mixtures thereof in various proportions without limitation. Preferably n-hexane.

As used herein, a solvent is any liquid substance capable of dissolving compound of VI or a salt thereof.

As used herein, the term "antisolvent" means a liquid in which a compound is poorly soluble. The addition of an antisolvent to a solvent reduces the solubility of a compound.

As used herein a mixture of solvents refers to a composition comprising more than one solvent.

The isolated solid (7-Methoxy-1-naphthyl)ethanamine (VI) of the present invention is useful as a reference marker for agomelatine (I). As such, it may be used in order to detect the (7-Methoxy-1-naphthyl)ethanamine impurity in a agomelatine sample.

The starting intermediate compounds of formula III and the intermediate compound of formula VI can be prepared either by the processes reported in the art or by the process disclosed in our PCT application PCT/IN2011/000003.

The intermediate compounds of formula (II) obtained by the processes of present invention can be converted into final active compound agomelatine of formula I by processes described in the art. Illustratively, by the process described in U.S. Patent No. 7,544,839.

These processes are especially valuable for the following reasons: it makes it possible to obtain the compound of formula (I) in excellent yields on industrial scale.

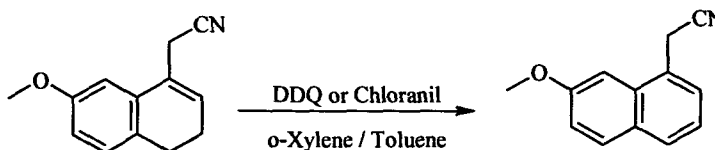
The processes for the preparation of intermediates of agomelatine of the present invention is simple, eco-friendly, robust, reproducible, cost effective and well amenable on commercial scale.

SLLPCT16

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

EXAMPLES

5

Preparation of (7-Methoxy-1-naphthyl)acetonitrile

10

Example-1: 15 g. (0.07 mol) of (7-Methoxy-3,4-dihydro-1-naphthyl)acetonitrile, 24 g. (0.09 mol) of Chloranil (2,3,5,6-Tetrachlorocyclohexa-2,5-diene-1,4-dione) and 600 ml. of O-xylene were charged in a clean and dry 4 neck R.B. Flask and heated to reflux temperature for about 8 hrs. The resultant reaction mixture was cooled to about 30°C and filtered. The filtrate was washed with 3x50 ml of 10% w/v sodium hydroxide solution and 2x50 ml of water. The solvent was distilled completely under vacuum, the solid separated was recrystallized from ethanol and water mixture in 8:2 ratio to afford 13 g. (88%) of the title compound with a chemical purity 99%.

15

Example-2: The process is same as described in above example 1 by using toluene instead of o-xylene to yield 13.5 gr. (91%) of the title compound with a chemical purity 99%.

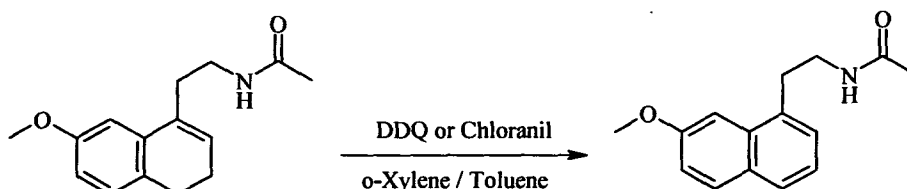
20

Example-3: 5 g. (0.02 mol.) of (7-Methoxy-3,4-dihydro-1-naphthyl)acetonitrile, 7.5 g. (0.03 mol.) of 2,3-Dichloro-5,6-dicyano-benzoquinone (DDQ) and 200 ml. of O-xylene or toluene were charged in a clean and dry 4 neck R.B. Flask and heated to reflux temperature for about 2 hrs. The resultant reaction mixture was cooled to about 30°C and filtered. The filtrate was washed with 3x25 ml. of 10% w/v sodium hydroxide solution and 2x25 ml. of water. The solvent was distilled completely under vacuum and the resulted solid residue was recrystallized from ethanol/ and water mixture in a ratio of 8:2 to yield 4.5 gr. (91%) of the title compound with a chemical purity 99%.

25

30

SLLPCT16

Preparation of N-[2-(7-Methoxy-1-naphthyl) ethyl]acetamide

- 5 **Example-4:** 5 g. (0.02 mol) of N-[2-(7-Methoxy-3,4-dihydro-1-naphthyl)ethyl]acetamide, 6 g. (0.03 mol.) of 2,3-Dichloro-5,6-dicyano-benzoquinone (DDQ) and 200 ml. O-xylene or toluene were charged in a clean and dry 4 neck R.B. Flask and heated to reflux temperature for about 4 hrs. The resultant reaction mixture was cooled to about 30°C and filtered. The filtrate was washed with 3x30 ml. of 10% w/v of sodium hydroxide solution and 2x30 ml. of water.
- 10 After removal of the solvent by evaporation, the resultant solid residue was recrystallized from an ethyl acetate and n-hexane mixture in a ratio of 1:2 to provide 4.5 g. (90%) of the title compound with a chemical purity exceeding 99%.

- Example-5:** 15 g. (0.06 mol) of N-[2-(7-Methoxy-3,4-dihydro-1-naphthyl)ethyl]acetamide, 19.5 g. (0.08 mol.) Chloranil (2,3,5,6-Tetrachlorocyclohexa-2,5-diene-1,4-dione) and 600 ml.
- 15 of O-xylene were charged in a clean and dry 4 neck R.B.Flask and heated to reflux temperature for about 5 hrs. The reaction mixture was cooled to about 30°C and filtered. The filtrate was washed with 3x50 ml. of 10%w/v sodium hydroxide solution and 3x50 ml. of water. The solvent was distilled completely under vacuum and the resultant solid residue was recrystallized from ethyl acetate and n-hexane mixture in 1:2 ratio to yield 12 g. (81%) of the
- 20 title compound with a chemical purity exceeding 99%.

Example-6: The process is same as described in above example 5 but using toluene instead of o-xylene to yield 13 g. (87%) of the title compound with a chemical purity exceeding 99%.

Example-7: Preparation of (7-Methoxy-1-naphthyl)acetonitrile using selenium

- 10g, (0.05 mol.) of (7-Methoxy-3,4-dihydro-1-naphthyl)acetonitrile and 6 g. (0.07
- 25 mol.) of selenium metal powder were charged into a clean and dry 4 neck R.B.Flask and heated to about 220 °C for about 3 hrs. The reaction mixture was allowed to reach about 65 °C and 30 ml. of water and ethanol mixture in ratio of 2: 8 was added. The resultant reaction mass was heated to reflux for 30 min. The hot reaction mixture was treated with 2 gr. of charcoal and filtered. The filtrate obtained was cooled to about 0°C for about 1 hr. The solid separated was
- 30 filtered to obtain 6.5 g. (66%) of the title compound with a chemical purity 98%.

SLLPCT16**Example-8: Preparation of N-[2-(7-Methoxy-1-naphthyl)ethyl]acetamide using selenium**

10g. (0.04mol.) of N-[2-(7-Methoxy-3,4-dihydro-1-naphthyl)ethyl]acetamide and 5 g. (0.06 mol.) of selenium metal powder were charged into a clean and dry 4 neck R.B.Flask and heated to about 220 °C for about 4 hrs. The resultant reaction mixture was allowed to reach about 65°C and extracted with 100 ml. of ethyl acetate. The solvent was removed completely by evaporation, the solid residue obtained was recrystallized from a mixture of ethyl acetate and n-hexane in a ratio of 1:2 to provide 6 gr. (61%) of the title compound with a chemical purity exceeding 99%.

Example-9: Preparation of (7-Methoxy-1-naphthyl)ethanamine in solid form

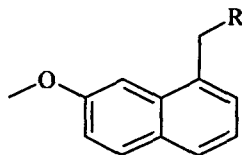
To 50g. (0.21 mol.) of (7-Methoxy-1-naphthyl) ethanamine hydrochloride solution in 250 ml. water present in a clean and dry R.B.Flask 5 gr. of charcoal was charged. The reaction mixture was stirred at about 30°C for about 15 min. and then filtered on a celite bed. Sodium carbonate (34 gr., 0.32 mol) was added to the filtrate obtained. Then the reaction mixture was stirred at about 30°C for about 15 min. and further cooled to about 10°C for about 30 min. The separated solid was filtered and the solid obtained was washed with 50 ml. of distilled water. 70 ml. of ethyl acetate was added to the wet solid and stirred at about 0 °C for about 30 min. The solid obtained was filtered and rinsed with ethyl acetate to afford 30 g. of the title compound.

M. R.: 101-104 °C. Purity by H.P.L.C: 99.85%.

SLLPCT16

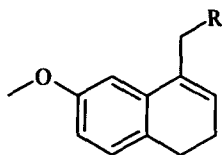
We Claim:

1). A process for the preparation of intermediate compound of II



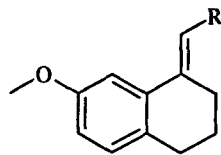
II

- 5 Where R is $C\equiv N$, $CH_2-NH-COCH_3$
 comprising:
 subjecting the compound of formula III



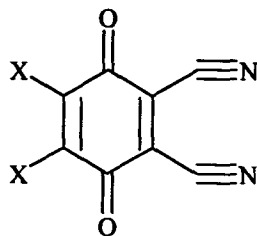
III

or



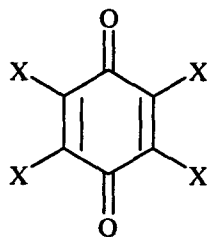
III

- Where R is same as defined above
 10 to aromatization by reacting with a quinone derivative of formula IV



IV

Where X is halogen atom (F, Cl, Br, I)
 or formula V



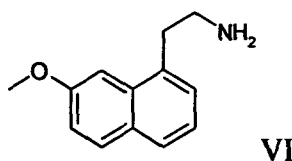
V

15

Where X is same as defined above
 or using selenium metal to afford the compound of formula II.

SLLPCT16

- 2) The process of claim 1, wherein the aromatization reagents is selected from the group consisting of quinone derivatives of formula IV or V where X is halogen atom like F, Cl, Br and I including DDQ, p-chloranil, p-bromanil, p-floranil, 2,3-dibromo-5,6-dicyano benzoquinone, 2,3-dicyano-4-chlorobenzoquinone, 2,3-dicyanobenzoquinone and other quinone derivatives like 1,2-benzoquinones, 1,3-benzoquinones, o-chloranil, o-floranil, o-bromanil or mixtures thereof, preferably DDQ or p-chloranil.
- 3) The process of claim 1, wherein the organic solvent used is selected from the group consisting of halogenated solvents like dichloromethane, ethylene dichloride, chloroform, chlorobenzene, esters like ethyl acetate, isopropyl acetate, tertiary butyl acetate, ethers like tetrahydrofuran, 1,4-dioxane, diethyl ether, hydrocarbons like n-hexane, n-heptane, cyclohexane, toluene, o-xylene, p-xylene or mixtures thereof, aprotic polar solvents like N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), N,N-dimethylacetamide (DMA), N-methyl pyrrolidone (NMP), ethylene glycol or mixtures thereof, preferably toluene or o-xylene.
- 4) The process of claim 1, wherein the reaction is performed optionally in the absence of solvents when quinone derivatives are being used.
- 5) The process of claim 1, wherein the reaction is carried out at a temperature from about 50°C to about reflux temperatures of the solvents used and the time period is from about 1 hour to about 10 hours when quinone derivatives are being used.
- 6) The process of claim 1, wherein the conversion of compound of formula III to the compound of formula II using selenium is carried out in the absence of solvents.
- 7) The process of claim 1, wherein the reaction is carried out using selenium at a temperature from about 100°C to about 220°C and the time period is from about 1 hour to about 10 hours.
- 8) Isolated solid (7-Methoxy-1-naphthyl)ethanamine compound of structural formula VI as freebase

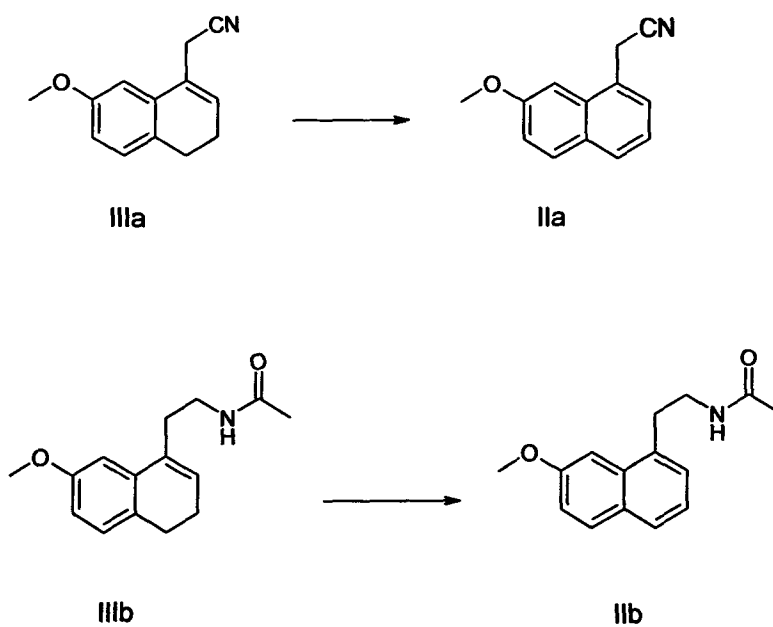


- 9) The process of claims 1 and 8, wherein the compounds are used as intermediates in the preparation of active naphthalene derivatives like agomelatine (I).

SLLPCT16

Symeds labs limited

Fig.1. of 1



5

10

15

Fig. 1

20

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN 11/00203

A. CLASSIFICATION OF SUBJECT MATTER
 IPC(8) - A01N 31/14; A61K 31/075 (2011.01)
 USPC - 514/721

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 USPC: 514/721

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
 USPC: 514/678, 681-683, 715, 717-718 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 PubWEST (USPT, PGPB, EPAB, JPAB), Google Patents/Scholar
 Search Terms Used: agomelatine, dihydroxynaphthalene, aromatization, DDQ, chloranil, solvent, selenium

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2005/0182276 A1 (Souvie et al.) 18 August 2005 (18.08.2005) para [0018], [0023]-[0025], [0030]	8 ----- 1-7
Y	US 6,020,513 A (Bryant et al.) 01 February 2000 (01.02.2000) col 7, ln 13-45, 49-62	1-5
Y	US 4,764,635 A (Ramachandran et al.) 16 August 1988 (16.08.1988) col 2, ln 33-68, col 3, ln 3-21	1, 4, 6-7

☐ Further documents are listed in the continuation of Box C.



* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

25 August 2011 (25.08.2011)

Date of mailing of the international search report

01 SEP 2011

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
 P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN 11/00203

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 9
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.